In re Patent Application of

ARMOUR et al.

Serial No. 09/674,857

Filed: November 7, 2000

Title: BINDING MOLECULES DERIVED FROM IMMUNOGLOBULINS WHICH DO NOT TRIGGER COMPLEMENT MEDIATED LYSIS

Atty Dkt. 620-117
C# M#

Group Art Unit: 1644

Examiner: Huynh, P.

Date: April 8, 2002

4/24/02

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

RESPONSE/AMENDMENT/LETTER

This is a response/amendment/letter in the above-identified application and includes an attachment which is hereby incorporated by reference and the signature below serves as the signature to the attachment in the absence of any other signature thereon.

Fees are attached as calculated below:

Total effective claims after amendment 0 minus highest number previously paid for 20 (at least 20) = 0 x $ 18.00	$	0.00
Independent claims after amendment 0 minus highest number previously paid for 3 (at least 3) = 0 x $ 84.00	$	0.00
If proper multiple dependent claims now added for first time, add $280.00 (ignore improper)	$	0.00
Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s) ($110.00/1 month; $400.00/2 months; $920.00/3 months)	$	920.00
Terminal disclaimer enclosed, add $ 110.00	$	0.00
☐ First/second submission after Final Rejection pursuant to 37 CFR 1.129(a) ($740.00) ☐ Please enter the previously unentered , filed ☐ Submission attached	$	0.00
Subtotal	$	**920.00**
If "small entity," then enter half (1/2) of subtotal and subtract ☐ Applicant claims "small entity" status. ☐ Statement filed herewith	-$	0.00
Rule 56 Information Disclosure Statement Filing Fee ($180.00)	$	0.00
Assignment Recording Fee ($40.00)	$	0.00
Other:		**0.00**
TOTAL FEE TO BE DEBITED	$	**920.00**

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140. A duplicate copy of this sheet is attached.

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Atty Dkt.: 620-117

Date: April 8, 2002

To: Examiner Huynh, P. - Group: 1644
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Number of Pages (including cover sheet): 31
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Tabitha A. Trice
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ATTACHMENT/S: **OFFICIAL RESPONSE W/PTO-1449 FORM AND REFERENCES**

MESSAGE:

In re PATENT APPLICATION OF:

ARMOUR et al.
Serial No.: 09/674,857
Filed: November 7, 2000
For: BINDING MOLECULES DERIVED FROM IMMUNOGLOBULINS WHICH DO NOT TRIGGER COMPLEMENT MEDIATED LYSIS

#15

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF

ARMOUR et al. Atty. Ref.: 620-117

Serial No.: 09/674,857 Group Art Unit: 1644

Filed: November 7, 2000 Examiner: Huynh, P.

For: BINDING MOLECULES DERIVED FROM IMMUNOGLOBULINS WHICH DO NOT TRIGGER COMPLEMENT MEDIATED LYSIS

* * * * *

April 8, 2002

RESPONSE

Hon. Commissioner of Patents
and Trademarks
Washington, DC 20231

Sir:

In response to the Examiner's requirement for restriction, set forth in the Office Action dated December 6, 2001 (the period for response having been extended up to April 6, 2002 by submission of the required petition and fee herewith), Applicants elect the subject matter of Group II (claims 1-15 and 30 based on FOG1 and RhD) for prosecution in this application. The election is made with traverse and the Examiner is urged to reconsider the requirement for restriction for the reasons that follow.

At the outset, Applicants direct attention to the fact that the manner in which the Examiner has restricted the

subject invention deprives Applicants of an opportunity to prosecute a generic claim (e.g., a claim of the entire scope of claim 1). Additionally, restriction of the case into 61 different inventions places an intolerable financial burden on Applicants. The filing fees alone approximate $45,000. A requirement that so profoundly disadvantages an applicant is clearly improper.

As basis for the restriction requirement, the Examiner states:

> "Since Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have single general inventive concept and lack unity of invention."

The "prior art" to which the Examiner refers is Cole et al (J. Immunology 159:3613 (1997)). Applicants submit that the Examiner's reliance on Cole et al is not well founded.

As indicated on pages 6-7 of the subject application, the present invention provides a binding molecule that minimizes undesirable activities (for example, CDC) mediated by the IgG C domain – while retaining desirable activities mediated by the IgG C domain (for example, neonatal transport of IgG and inhibition of cellular responses). These latter activities are effected *inter alia* through the FcRn and FcγIIb receptors. Thus the present

invention provides an approach to altering the balance of binding to activatory versus inhibitory Fc receptors.

The invention is based on the use of chimeric antibody regions in which specific residues are altered, importantly, the amino acids incorporated are selected only from IgG parent molecules. The Examples provided in the subject application make it clear that chimeric antibodies of the invention, having residues that are not 'alien' to native IgG's, have combinations of activities not demonstrated or predicted by the parent antibodies, or the mutant antibodies of the art.

Cole et al differs from the present invention conceptually, functionally and structurally.

Conceptual Distinction

A detailed reading of Cole et al shows it is not concerned with natural effector functions of antibodies, for example, the triggering of cytotoxicity through Fc receptors on actual "effector" cells. In Cole et al, modification in the antibody are made to reduce the mitogenic effects on the target T-cells bearing the CD3 antigen to which the antibody is specific. These effects are attributed to the ability of the Fc receptors in Cole et al to bridge or to cross-link the CD3-bearing T cell

bound by the antibody and a further Fc receptor-bearing cell, thereby eliciting a mitogenic signal that activates the T-cell - it is the further "accessory" cell that has the Fc receptor. In the first paragraph of the introduction of Cole et al (last sentence) the authors indicate that the role of Fc receptors in their system is analogous to immobolizing the antibody on a plastic surface. This clearly has nothing to do with Fc triggered **effector functions** of a cytotoxic antibody, as in the case of the present invention.

Functional Distinction

The Examiner states at page 11 of the Action that the mutants of Cole et al bind FcγRIIb. In fact, this is not the case.

The present specification describes the differences between FcγIIb and FcγIIa receptors (see pages 2-3, bridging; also pages 12-13). The claims of the subject application concern only the former.

The only data in Cole et al directly relating to FcγRII is the FcγRII-dependent T-cell retargeting assay using K562 cells. These express only FcγRIIa of both HR (131R) and LR (131H) allotypes (see page 3615 under "FcγRII-dependent T-

cell retargetting assay"). Further evidence that FcγIIb is not expressed on these cells comes from the cited reference [23], Warmerdam et al (1991) J. Immunol 147: 1338) (copy attached). This reference shows that binding of human IgG1, 2 and 3 to these cells is almost completely inhibited by the monoclonal antibody IV.3 (see Figure 1 therein). As demonstrated in a later paper, this monoclonal does not bind well to FcγIIb (Wannerdam et al (1993) Int. Immunol. 5:129-247, copy attached - see, e.g., page 241, second column, 7th line from bottom; page 244, first column, 8th line from bottom; page 244, second column, 7th line from bottom; also Figure 2).

The data in the retargeting assay indicate that the mutant tested does not bind to the K562 cells, that is, does not bind the FcγII receptors that are present, contrary to the requirements of the present claim.

Summarizing, there is no reference to FcγIIb in Cole et al, and it would be clear to the reader that the article concerns only the FcγRIIa form of the FcγRII receptors, which itself may not even be bound.

Structural Distinction

As regards the amino acid substitutions of Cole et al, they are not encompassed by the present claims.

It is acknowledged that Cole et al teaches certain antibody mutants (in their case, for the purpose of reducing the mitogenicity of anti-CD3 antibodies). Some of these mutants are modified in regions corresponding to one of those used in the present invention. However, Cole et al does not teach that the amino acids used should be specifically selected only from IgG parent molecules. As is very clearly shown in Table 1, page 3615 (referred to by the Examiner), most of the substitutions made in the 234-237 region are:

- Ala at position 234
- Glu at position 235
- Ala at position 237

None of these amino acids is taken from 'other' human IgGs (see first four rows of the table, which give the wild-type sequences). Indeed, generally speaking, Cole et al actually teaches away from the present invention in advocating the use of such 'non-natural' amino-acids for all of the mutants (M1 -M5), with which the paper was primarily concerned.

In one case (IgG4 mutant AA) there is a mutation:

Leu -> Ala at position 237

Applicants acknowledge that Ala is found in IgG2. Nevertheless, claim 1 and dependent claims require:

> "...a chimeric effector domain which is derived from two or more human immunoglobulin heavy chain C_H2 domains including a first human immunoglobulin heavy chain C_H2 domain wherein **2, 3 or 4 amino acids** in at least 1 region of the C_H2 domain have been modified to the corresponding amino acids from a second, different, human immunoglobulin heavy chain C_H2 domain, wherein the region is selected from the 2 discrete regions numbered residues 233-236, and 327-331 in accordance with the EU numbering system..." (emphasis added).

As will be clear from the foregoing, IgG4 mutant AA of Cole et al has only a single amino acid found in a different immunoglobulin heavy chain C_H2 domain.

Importantly, the IgG4 mutant AA was prepared purely for comparison with those which form the main teaching of Cole et al (i.e., M1-M5 in the Table) (see 5th line from end of page 3615). It is absolutely clear that the use of even a single residue from another IgG was pure coincidence. 'Ala' is apparently proposed because it is a small 'neutral' residue, not because it is found naturally in a different IgG subclass. Indeed, this approach to substitutions is no more than the prior art methodology of

"ala scanning", as discussed, e.g., in Clark et al (1997) "IgG Effector Mechanisms" Chem. Immunol. 65:88-110 - of record, see page 98, line 12). The strategy is used to detect and destroy functions, not to balance stimulatory and inhibitory functions, as is the case in the present invention.

Cole et al is acknowledged in the present application (page 5, lines 1-9) and was provided by the present assignee to the IPEA (it is D5b therein) to ensure that it formed part of the IPE procedure. In the IPER it is acknowledged that none of the cited documents (including D5b) teach the combination of the functional requirement of FcRn\FcγIIb binding with the particular (amino acid) changes within the specified immunoglobulin regions.

Conclusions

In conclusion, Cole et al is unrelated to the problem solved by the present invention. Further, Cole et al:

(i) does not demonstrate the combinations of functions required by the claims (e.g., FcγIIb binding), and

(ii) does not teach the 2, 3 or 4 IgG-derived amino acid substitutions by which these functions are achieved, also as required by the claims.

Thus, Cole et al cannot be said to teach or suggest the present invention.

R13.1 & R13.2PCT:

All the claims and species have unity of the invention because they share a special technical relationship. The special technical feature which they share is the requirement that the binding molecules of all of claims 1 to 15 and 30:

(i) are capable of specifically binding FcRn and/or FcγRIIb, and,

(ii) have a chimeric effector domain that is derived from two or more human immunoglobulin heavy chain C_H2 domains, including a first human immunoglobulin heavy chain C_H2 domain wherein 2, 3 or 4 amino acids in at least 1 region of the C_H2 domain have been modified to the corresponding amino acids from a second, different, human

immunoglobulin heavy chain C_H2 domain, wherein the region is selected from the 2 discrete regions numbered residues 233-236, and 327-331, in accordance with the EU numbering system, and wherein in each case the human immunoglobulin is selected from IgG1, IgG2 and IgG4.

This combination of special technical features is not taught in the art, and embodies a single general inventive concept that unifies the claims.

Claims 16-20 are based generally on nucleic acids that encode the instant binding molecules. The sequence of amino acids in the binding molecules described above is, of course, an essential structural element of those molecules, and it is encoded by an exactly corresponding sequence of codons in the nucleic acids. Thus, the same special technical features are found in these claims.

Claims 21-22 and 23-29 concern the production of the binding molecules of claim 1, or having the same special technical features of claim 1, thus they also have unity of invention.

All of these groups are technically related, and clearly fall within the meaning of the examples given in Annex B in the PCT administrative instructions, or in MPEP at 1850.

The primers of claim 31 are novel and inventive by virtue of the fact that they are adapted for use in the claimed methods, and are in any case not suggested by the prior art.

For completeness, it is noted that the dependent claims include additional features that are inventive over the art, e.g., the use of the mutant antibodies (having the desired combination of activities taught in the application) to block effector functions of other allo- or auto-antibodies. However, such is not a ground for disunity under the applicable PCT rules (see Rule 13.4 PCT).

Other issues – improper grouping of claims

It will be clear from the foregoing that the requirement for restriction is based on a misinterpretation of Cole et al. However, for completeness, for following points are also made:

i) Group I + others: Campath – this binds CD52 (Fog binds RhD)

ii) Group X: Lutheran is not a hormone but a red cell antigen

iii) Groups XLVI and LIX: platelet GPVI has nothing to do with haemolytic disease but is concerned with

coronary artery disease (cf. Groups XLVII and LX).

Again, the Examiner is urged to reconsider the requirement for restriction, it is clearly improperly based. Should the Examiner refuse to rejoin the claims, Applicants reserve the right to petition the Commissioner to invoke his supervisory authority and to have the claims rejoined.

An early and favorable Action on the merits is awaited.

Respectfully submitted,

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